Alzheimer Disease (AD)

Comprehensive Case Presentation on Alzheimer Disease

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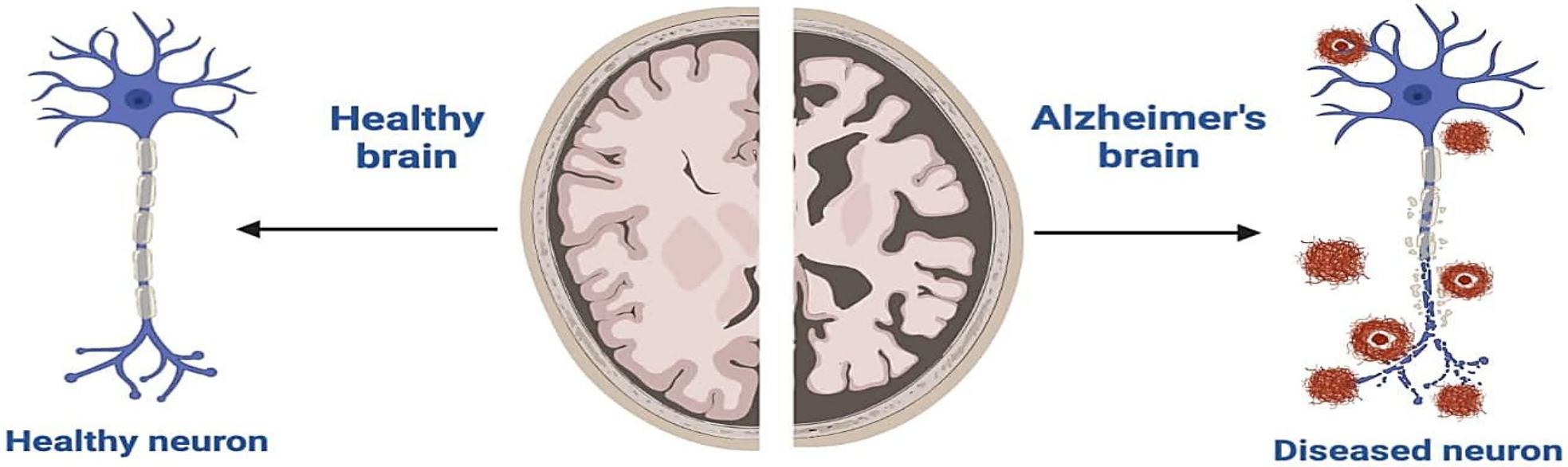
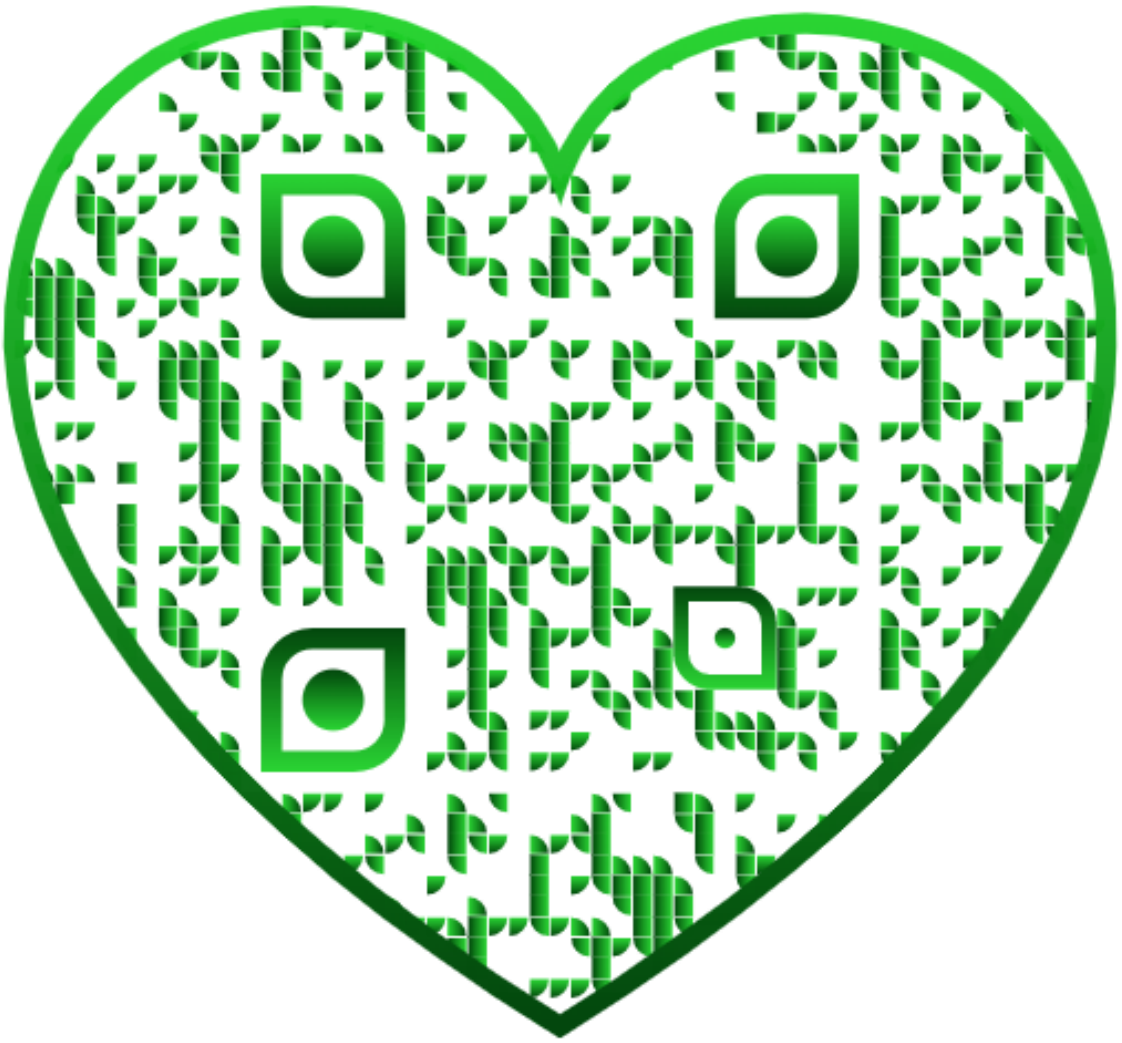




Introduction to Alzheimer Disease (AD)

- **Alzheimer Disease:** is **irreversible ,progressive neurodegenerative Disorder Characterized by**: **Gradual deterioration in cognition**, **Progressive memory loss**, **Deterioration of functional status** and **Behavioral disturbance** : **aggression , depression , emotional liability , motor hyperactivity**

- **Epidemiology:**

  - ✓ AD is the **most common cause of dementia**, accounting for **60% to 80% of cases.**
  - ✓ The **mean survival time** of persons with AD is **approximately 4 to 8 years from symptom onset.** However, **age at diagnosis, severity of AD, and other medical conditions** affect survival time.
  - ✓ The **exact pathophysiologic mechanisms underlying AD are not entirely known**, and **no cure exists**. Although drugs may reduce AD symptoms for a time, the disease is eventually fata**.**
  - ✓ Although **AD does not directly cause death**, it is **associated with an increase in risk factors** that often **contribute to death**, such as **senility, sepsis, stroke, pneumonia, dehydration, and decubitus ulcers**.

Etiology of Alzheimer's Disease (AD)

➢ **Risk Factors**:

- **Non-modifiable**: Age, family history, female gender, genetic predisposition.
- **Modifiable**: Vascular risks (diabetes, hypertension, heart disease, smoking).
- **Pathogenesis:** Errors in protein synthesis lead to **beta-amyloid (Aβ) accumulation**, **oxidative stress**, and **neuronal destruction**

➢ **Genetics**:

Early-onset AD	Late-onset AD
- **Occur (before age 60)** accounts for approximately **1% of cases** and is often **familial**, following an **autosomal dominant** pattern in 50% of cases. - Mutations in **three key genes**—**PSEN1** on chromosome **14**, **APP** on chromosome **21**, and **PSEN2** on chromosome **1**—lead to an **increased accumulation of amyloid beta (Aβ)** in the brain.	- **is sporadic and influenced by environmental factors**. - The **apo E gene on chromosome 19** is a major risk factor, with the **apo E4 allele** linked to an **earlier onset (by ~6 years)**. - However, since only **50% of patients carry apo E4**, it is a **risk marker, not a direct cause**.

Alzheimer Disease: Case Study

Case Study Introduction

- A man presents at the clinic with his 75-year-old mother complaining that his mother's memory is worsening. He complains that his mother is continuing to forget things, including paying the bills and emptying the cat's litter box. Three months ago, she was started on donepezil 5 mg, which was titrated to 10 mg. Her son organizes a weekly pillbox and helps administer the medications. The son asks if there is anything else his mother could take to help her memory.

Alzheimer Disease: Case Study

1. What education points about Alzheimer Disease would you provide to the son?

- AD is progressive, and while medications like Donepezil can slow symptom progression, they do not cure the disease.
- Establishing a structured routine and providing safety measures at home are critical.
- Importance of caregiver self-care and seeking support from community or online resources.

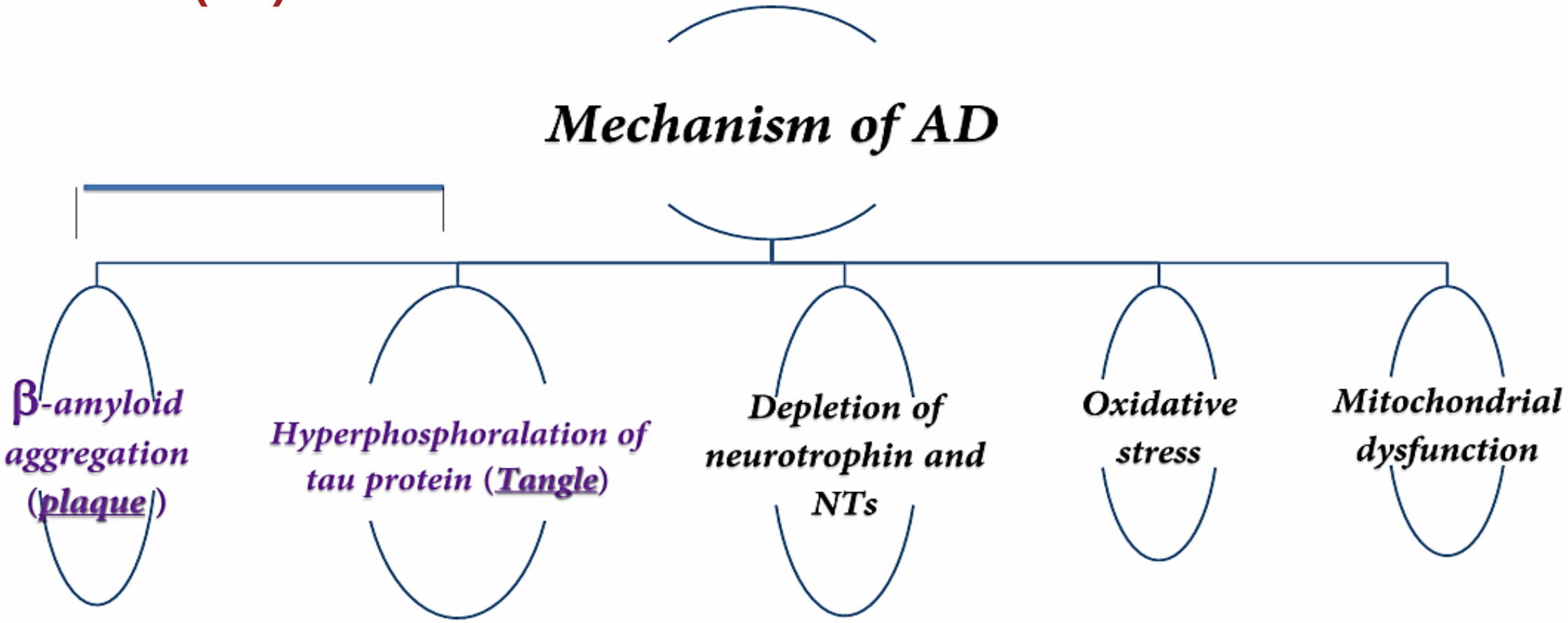
2. Where would you recommend the son find more information about Alzheimer disease?

1. The Alzheimer's Association website (www.alz.org).

- Local support groups, advocacy organizations, and healthcare providers specializing in dementia care.

Pathophysiology of Alzheimer's Disease

3. What are the main pathophysiological mechanisms underlying Alzheimer's Disease (AD)?



Clinical Presentation of Alzheimer's Disease

4. What are the key symptoms of Alzheimer's Disease?

CLINICAL PRESENTATION | **Alzheimer Disease**

General

- The patient may have vague memory complaints initially, or the patient's friends or family may report that the patient is "forgetful." Cognitive decline is typically gradual over the course of illness. Behavioral disturbances may be present in moderate stages. Loss of daily function such as dressing, bathing, and toileting is common in advanced stages.

Symptoms

Cognitive

- Memory loss (poor recall and losing items)
- Aphasia (circumlocution and anomia)
- Apraxia
- Agnosia
- Disorientation (impaired perception of time and unable to recognize familiar people)
- Impaired executive function

Neuropsychiatric

- Depression, psychotic symptoms (hallucinations and delusions)
- Behavioral disturbances (physical and verbal aggression, motor hyperactivity, uncooperativeness, wandering, repetitive mannerisms and activities, and combativeness)

Functional

- Inability to care for self (dressing, bathing, toileting, and eating)

Clinical Presentation of Alzheimer's Disease

5. What diagnostic tools and criteria are used to confirm Alzheimer's Disease?

❖ The **diagnosis of AD is based on clinical assessment**, supported by **cognitive tests, imaging, and laboratory studies:**

1. **Cognitive Tests**: MMSE, MoCA, and Mini-Cog for evaluating memory, attention, and executive function.

2. **Imaging**: **MRI or CT** to identify **structural brain changes** (e.g., hippocampal atrophy) Also PET scans for detecting amyloid and tau pathology.

3.Laboratory Tests:

✓ **Exclude reversible causes** (e.g., vitamin B12 deficiency, thyroid dysfunction).

- **The DSM-5 criteria** require evidence of cognitive decline interfering with independence in daily activities.
- **Biomarkers** (e.g cerebrospinal fluid amyloid/tau levels) are emerging tools for early detection.

Clinical Presentation of Alzheimer's Disease

- **These tools help screen, diagnose, and monitor cognitive decline in Alzheimer's Disease.**

Tool	Purpose	Duration	Key Components	Scoring	Key Points:
1- Mini-Mental State Examination (MMSE)	General cognitive function	10–15 min	Orientation, registration, attention, recall, language, visuospatial skills	30-26: normal 25-20: mild 19-10: moderate 9-0: severe	**Most widely used**; effective for **moderate-to-severe AD** but **less sensitive for early stages**
2- Montreal Cognitive Assessment (MoCA):	Mild cognitive impairment (MCI)	10–15 min	Memory, executive function, attention, visuospatial, abstraction, orientation	26–30: Normal; <26: Cognitive issues	**Superior for detecting early cognitive impairment**; covers executive and abstraction skills.
3- Mini-Cog	Quick dementia screening	3–5 min	3-word recall, clock-drawing test	0–2: Possible dementia 3–5: Normal	**Fast, practical for initial screenings**; ideal in primary care.

Clinical Presentation of Alzheimer's Disease

MMSE- Mini Mental Status Exam

	Instructions: Score one point for each correct response within each question or activity.	MAX Score	Score Date	Score Date	Score Date
1	**Orientation:** What is the (year) (season) (date) (month)?	5			
2	Where are we now? (state) (country) (town/city) (hospital) (floor)	5			
3	**Registration:** Repeat (immediately) 3 objects: Apple ____ Table____ Penny____	3			
4	**Attention/Calculation:** Serial 7's or spell WORLD backwards	5			
5	**Recall:** Remember 3 objects at 2 minutes: Apple ____ Table ____ Penny____	3			
6	**Language:** Name 2 simple objects (watch and pencil)	2			
7	Repeat the phrase "no if's, ands, or buts".	1			
8	Three stage command. "Take the paper in your right hand, fold it in half, and put it on the floor."	3			
9	Please read this and do what it says: "Close your eyes" (attached page)	1			
10	Write a sentence about anything. (attached page, must include a noun and a verb)	1			
11	**Visual-Spatial:** Copy design (attached page)	1			
	TOTAL	30			

MINI-MENTAL STATE EXAM

10

CLOSE YOUR EYES

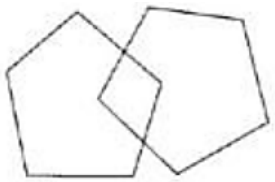


TABLE 73-2 Stages of Alzheimer Disease

Mild (MMSE score 26–21)	Patient has difficulty remembering recent events. Ability to manage finances, prepare food, and carry out other household activities declines. May get lost while driving. Begins to withdraw from difficult tasks and to give up hobbies. May deny memory problems.
Moderate (MMSE score 20–10)	Patient requires assistance with activities of daily living. Frequently disoriented with regard to time (date, year, and season). Recall of recent events is severely impaired. May forget some details of past life events and names of family and friends. Functioning may fluctuate from day to day. Patient generally denies problems. May become suspicious or tearful. Loses ability to drive safely. Agitation, paranoia, and delusions are common.
Severe (MMSE score 9–0)	Patient loses ability to speak, walk, and feed self. Incontinent of urine and feces. Requires care 24 hours a day, 7 days a week.

MMSE, Mini-Mental State Examination.

General Approach to Treatment of AD

6. How would you address the son's question regarding the pharmacologic management of his mother's Alzheimer Disease?

- **Optimize therapy:** Confirm that donepezil has been appropriately titrated to 10 mg daily and explain its mechanism of action as an acetylcholinesterase inhibitor improving cholinergic neurotransmission.

- **Consider memantine:** If not already initiated, memantine 10 mg twice daily (NMDA receptor antagonist) can be added for moderate-to-severe AD to help reduce excitotoxicity and improve symptoms.

- **Set realistic expectations:** Explain that while these medications may stabilize cognitive symptoms, they will not reverse the disease.

- **Monitor adherence:** Stress the importance of proper medication administration and regular follow-ups to adjust treatment if needed.

General Approach to Treatment of AD

Case Study Con. Six-Month Follow-Up:

The patient returns to the clinic in 6 months. She has been on donepezil 10 mg daily and memantine 10 mg twice daily. Her memory symptoms have slowed in their decline, but recently she has been agitated at bedtime and talking to her deceased sister. The son is particularly concerned about the symptoms and wants to know what he could do to help. The patient's record is as follows:

PMH: Diabetes mellitus since age 51 (well controlled until last year when she became confused about when to take her medication); hypertension (treated for 23 years, well controlled, has been hypotensive on a few occasions recently during physicals); osteopenia (last bone mineral density test 12 months ago [T-score = −1.2] on therapy); hypercholesterolemia (last cholesterol panel 12 months ago showed well-controlled levels in normal range, on therapy)

FH: Father died of myocardial infarction at age 76; mother died of breast cancer at age 79
SH: Lives with wheelchair-bound husband; son lives across street and checks in daily; denies drinking alcohol or smoking

General Approach to Treatment of AD

Meds: Metformin 500 mg orally twice daily; insulin glargine 18 units subcutaneously at bedtime; hydrochlorothiazide 25 mg orally once daily in the morning; lisinopril 20 mg orally once daily in the morning; calcium carbonate and vitamin D 600 mg/200 international units orally twice daily with lunch and dinner; atorvastatin 10 mg orally once daily with dinner; donepezil 10 mg orally daily and memantine 10 mg orally twice daily
ROS: (+) Weight loss of 6.3 kg (14 lb) since last visit; (−) N/V/D, change in appetite, heartburn, chest pain, or shortness of breath

PE:
VS: BP 111/72 mm Hg supine, P 79 beats/min, RR 16 breaths/ min, T 37°C (98.6°F)
Gen: Poorly groomed, thin woman looks as stated age
Neuro: Folstein Mini-Mental State Examination score 20/30 (suggestive of **moderate** dementia) and MoCA score 18/30 (suggestive of **moderate** dementia); disoriented to month, date, and day of week, clinic name and floor; poor registration with impaired attention and short-term memory; good language skills but problems with commands.

CT Scan: Mild-to-moderate generalized cerebral atrophy

General Approach to Treatment of AD

7. What are the Therapeutic Goals for initial pharmacologic management AD?

I. **The primary goal of treatment in AD:** is delaying disease progression and preserve patient function for as long as possible.

II. **Secondary goals include** treating psychiatric and behavioral symptoms that may occur during the course of the disease.

❖ General Approach to Treatment

- ✓ Prior to initiating treatment for AD, a thorough **medication review should be completed**.
- ✓ There are **four agents approved for the treatment of AD, but none are curative or known to directly reverse the disease process**; donepezil, rivastigmine, galantamine, and memantine.
- ✓ Treatment of AD includes **education, communication, and planning** with the **patient's family/caregiver**.
- ✓ Treatment options, **legal and financial decisions**, and **course of the illness should be discussed with the patient and family members..**

General Approach to Treatment of AD

8. What nonpharmacologic and pharmacologic interventions could be recommended for the agitation and psychosis?

1. Nonpharmacologic Interventions:

- The life of a patient with AD must become progressively simpler and more structured as the disease progresses, and the caregiver must learn to keep requests and demands on the patient simple. Basic principles in the treatment of patients with AD are shown in **Table 30–4.**

Table 30–4

Basic Principles in the Management of Patients with AD

- Use a gentle, calm approach to the patient
- Provide reassurance when needed
- Empathy with the patient's concerns
- Use distraction and redirection
- Maintain daily routines
- Provide a safe environment
- Provide daytime activities
- Avoid overstimulation
- Use familiar decorative items in the living area
- Bring abrupt declines in function and the appearance of new symptoms to professional attention

Pharmacologic treatment for AD

2. **Pharmacologic Interventions:** (**Symptom Control, Not Curative**)

- **The current gold standard of treatment for cognitive symptoms includes :**
  I. Cholinesterase (ChE) inhibitor (**Donepezil, Rivastigmine, Galantamine**)
  II. NMDA antagonist (**Memantine**)
  III. Anti-amyloid Monoclonal Antibody (**Aducanumab**)

- Additionally, **psychiatric and behavioral symptoms** that occur during the course of the disease should be treated as they occur.

Table 30–5

Treatment Algorithm for Cognitive Symptoms of AD

1. Patient diagnosed with AD
2. Assess all comorbid medical disorders and medication therapies that may affect cognition
3. Rule out comorbid depression
4. Evaluate for pharmacotherapy based on illness stage
   a. Mild AD: Acetylcholinesterase inhibitor
   b. Moderate-to-severe AD: Acetylcholinesterase inhibitor, memantine, or combination acetylcholinesterase inhibitor and memantine
5. Deteriorating Mini-Mental State Examination (MMSE) score > 2–4 points after 1 year: Change to a different acetylcholinesterase inhibitor
6. Stable MMSE: Continue regimen
7. Treat behavioral/noncognitive symptoms associated with AD as they arise

Pharmacologic treatment for AD

I - Treatment of cognitive symptoms

- Managing **blood pressure, cholesterol, and blood sugar** may reduce the risk of developing AD and **prevent the worsening of dementia** in patients with AD.

- Successful treatment reflects a **decline of less than 2-4 points each year** on the **MMSE score.**

A. Cholinesterase inhibitors: donepezil, rivastigmine, galantamine.

- They are **indicated in mild to moderate AD**, while **donepezil** is also indicated **in severe AD**.
- If the decline in MMSE score is **more than 2-4 points after treatment for 1 year** with the initial agent, it is **reasonable to change to a different cholinesterase inhibitor**.
- **Side effects: gastrointestinal symptoms** (nausea, vomiting, and diarrhea, especially with Rivastigmine). Other **cholinergic side effects are dose-related** and include: urinary incontinence, dizziness, headache, syncope, bradycardia, muscle weakness, salivation, and sweating.
- Concurrent use of **anticholinergic medications with cholinesterase inhibitors** should be avoided.

Pharmacologic treatment for AD

B. NMDA antagonist: Memantine (Namenda)

- It **blocks glutamatergic neurotransmission** by antagonizing **N-methyl-D-aspartate receptors**, which may prevent, and **It is indicated for treatment of moderate to severe AD**.
- It is initiated at **5 mg/day and increased weekly by 5 mg/day** to the **effective dose of 10 mg twice daily**. Dosing must be **adjusted in patients with renal impairment**.
- Well tolerated, and side effects include: **constipation, confusion, dizziness, hallucinations, headache, cough, and hypertension**.

C. Anti-amyloid Monoclonal Antibody: Aducanumab

- Aducanumab **binds to aggregated forms of amyloid in the brain,** which has been hypothesized to **reduce the likelihood of cerebral edema or micro hemorrhage.**
- Aducanumab, was controversially **approved under this accelerated pathway for use in MCI due to AD and mild AD.**
- Aducanumab represent a **first-of-its-kind treatment for AD**

Pharmacologic treatment for AD

D. Other Potential Treatment Approaches

- **Vitamin E** can be **used for prevention of AD but not treatment** (**greater than 400 IU/day is not recommended**).

- **Ginkgo biloba** should **not be used in individuals taking anticoagulants** or **antiplatelet drugs**, and should be **used cautiously in those taking NSAIDs**.

- **Caprylidene**: can be used as an **energy source** for AD patients to generate ATP and **increase pools of acetylcholine**.
  - Dose: **40-g powder packets**. One packet can be **mixed with 120–240 mL liquid** and dosed **once daily after a meal.**

Pharmacologic treatment for AD

Table 30–6

Dosing Strategies for Cognitive Agents

	Donepezil (Aricept)	Rivastigmine (Exelon)	Galantamine (Razadyne)	Memantine (Namenda, Namenda XR)	Memantine +Donepezil (Namzaric)
Starting dose	5 mg daily in the evening	Oral: 1.5 mg twice daily Patch: 4.6 mg/24 hour applied daily	IR: 4 mg twice daily ER: 8 mg daily in the morning	IR: 5 mg daily ER: 7 mg daily	7 mg/10 mg (if patient is stabilized on donepezil and not currently on memantine); 28 mg/10 mg (if patient is stabilized on memantine and donepezil)
Maintenance dose	5–23 mg daily	Oral: 3–6 mg twice daily Patch: 9.5 mg/24 hour applied daily	IR: 8–12 mg twice daily ER: 16–24 mg daily	IR: 10 mg twice daily ER: 28 mg daily	28 mg/10 mg daily
Time between dose adjustments	4–6 weeks between 5 and 10 mg increment; 3 months between 10 and 23 mg increment	Oral: 2 weeks Patch: 4 weeks	4 weeks	1 week	1 week
Dosage adjustments for renal or hepatic impairment	None	Moderate-to-severe renal impairment, mild-to-moderate hepatic impairment, or low body weight (< 50 kg): consider a maximum dose of 4.6 mg/24 hour (not studied in hepatic impairment)	Do not exceed 16 mg for moderately impaired hepatic or renal function; do not administer in severe renal or hepatic impairment	Severe renal impairment: target maintenance dose of 5 mg twice daily or 14 mg daily	Severe renal impairment: 14 mg/10 mg daily

Pharmacologic treatment for AD

II - Treatment of behavioral symptoms

A. Antipsychotics

- Prescribing of antipsychotics in AD **should be restricted to patients with severe symptoms not responding to other measures**, and treatment should be tapered as early as possible.

- **A meta-analysis of 16 trials** demonstrated the efficacy of **aripiprazole, risperidone, olanzapine, and quetiapine over placebo**; however, they were associated with a higher risk of adverse medication reactions.

- The American Psychiatric Association (APA) guidelines **recommend tapering and discontinuing the antipsychotic after 4 weeks at an adequate dose if no clinical benefit is seen**. If benefit is seen, an attempt to **taper should be made 4 months after initiation**, to reduce risk of harm as original need for the medication may change .

Pharmacologic treatment for AD

II - Treatment of behavioral symptoms

B. Antidepressants

- Depression and dementia have many symptoms in common, and the **diagnosis of depression can be difficult**, especially later in the course of AD.
- **Treatment with a SSRI** is usually initiated in depressed patients with AD.
- **Best evidence** is for **sertraline** and **citalopram** to treat depressed patients associated with AD. However, a recent trial suggested a **lack of benefit of sertraline and mirtazapine** compared with **placebo** and an increased risk of adverse effects.
- **Paroxetine** causes more anticholinergic side effects than the other **SSRI**.
- Although probably equally effective, the **tricyclic antidepressants** are usually **not recommended**.

General Approach to Treatment of AD

9. What do you recommend with regard to her current Donepezil and Memantine treatment?

- **Continue current treatment:** Since the patient is already on donepezil 10 mg daily and memantine 10 mg twice daily with stabilized cognitive symptoms, it is recommended to continue both therapies as they are the gold standard for moderate AD.

- **Monitor side effects:** Closely monitor for adverse effects such as gastrointestinal symptoms (donepezil) or dizziness/confusion (memantine). Ensure proper adherence to the medication regimen.

- **Evaluate effectiveness:** Use tools like MMSE or MoCA to periodically assess cognitive function and monitor the progression of symptoms.

Alzheimer Disease: Case Study Cons

Twelve-Month Follow-Up: End..

- The patient returns to the clinic for follow-up 6 months later. Her son states her memory has progressed significantly. Her current MoCA score is now 14/30. The addition of risperidone 0.5 mg at bedtime helped with her agitation, but she has significant symptoms that appear late in the afternoon on most days, especially if they have visitors to the house. Recently, she went outside and wandered off the property resulting in a brief police search to find and return her home. Her son would like to know if there are any other choices to help treat his mom.

Evaluation of therapeutic outcomes

10. What changes to the patient's current medications would you recommend?

- **Add nonpharmacologic interventions:** Optimize the environment to reduce evening triggers. Use tools like GPS trackers or door alarms to prevent wandering.

- **Consider melatonin:** Low-dose melatonin or trazodone can help manage evening agitation or sundowning.

- **Adjust antipsychotic therapy:**
  - If risperidone 0.5 mg at bedtime is well-tolerated, it may be continued. However, closely monitor for side effects (e.g., weight changes, sedation).
  - Consider tapering off antipsychotics once symptoms stabilize to avoid long-term risks.

Evaluation of therapeutic outcomes

- **Pharmacologic alternatives:**
  - **Cholinergic therapy:** Continue donepezil and memantine at current doses for cognitive stabilization.
  - **Mood stabilizers:** Evaluate mood stabilizers like carbamazepine or valproate if agitation becomes severe and persistent.

- **Monitor medical comorbidities:**
  - Evaluate the impact of weight loss (6.3 kg) and ensure it is not due to adverse medication effects or underlying conditions.
  - Assess blood pressure management and consider dose adjustments for antihypertensives (e.g., lisinopril, hydrochlorothiazide) to prevent further hypotension.

Evaluation of therapeutic outcomes

- Baseline assessment should define therapeutic goals and document **cognitive status, physical status, functional performance, mood, thought processes, and behavior**. Both the patient and caregiver should be interviewed.

- Objective assessments, such as the **MMSE for cognition** and the **Functional Activities Questionnaire for activities of daily living**, should be used to quantify changes in symptoms and functioning.

- The patient should be observed carefully for **potential side effects** of drug therapy. The specific side effects to be monitored and the method and frequency of monitoring should be documented.

- **Assessments for drug effectiveness, side effects, compliance, need for dosage adjustment, or change in treatment** should occur at least monthly.

- A treatment period of **6 months to 1 year** may be required to determine whether therapy is beneficial

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THANK YOU

FOR YOUR ATTENTION

Contact us for questions and more information

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